Current treatment strategies for obesity

Katarina Kos,
Christine Baker
& Sudhesh Kumar†

†Author for correspondence
Clinical Sciences Research Institute, University Hospital of Coventry & Warwickshire & Warwick Medical School, Coventry CV2 2DX, UK
Tel.: +44 247 657 4665
Fax: +44 247 657 4871
sudhesh.kumar@uhcw.nhs.uk

Obesity has become a threat to the health and economy of society worldwide and, if not contained, will be responsible for a dramatic increase in cardiorespiratory diseases and certain cancers. Though there is never any lack of trendy diets and slimming pill advertisements, many frustrated patients exhausted from individual efforts to lose weight, seek help from the medical professional. Which antiobesity treatments are effective? Can we stop the pandemic of obesity? This article gives a brief overview of the current status of obesity therapy and considers recent developments that may lead to new therapies.

Keywords:
antiobesity drugs, appetite-regulating hormones, bariatric surgery, body mass index, lifestyle, obesity, obesity related therapy

Obesity is a condition in which excess fat has accumulated to the extent that health is adversely affected [1]. The definition of obesity currently used by the World Health Organization (WHO) is based on the measurement of a person's body mass index (BMI). This is calculated by dividing the weight in kilograms by the square of the height in meters (kg/m^2). A BMI of greater than 30 kg/m^2 is classified as obesity and a range between 25 to 30 kg/m^2 as overweight. BMI correlates well with adiposity and mortality from obesity-related diseases. The degree to which adiposity affects health tends to differ between ethnic groups. Asian and Afro–Caribbean populations living in the UK are particularly affected by obesity and its consequences, such as diabetes. The International Obesity Task Force (IOTF) have developed revised guidelines for the range of BMI that may pose a health risk that takes into account the ethnic origin of the patient (**Table 1**). Visceral or abdominal fat is more harmful to health than subcutaneous fat and this has led to a recent trend for using waist circumference as well as BMI in epidemiologic studies (**Table 2**).

Incidence

The incidence of obesity has risen markedly worldwide in the last two decades and tripled in the UK [2]. More than half of the adult population of England and Wales are overweight or obese [101]. To have a high BMI may soon be the norm in much of Western Europe and the USA. Even in many developing countries, overweight and obesity is increasingly replacing the more traditional causes of ill health such as undernourishment and infectious diseases [1]. Within the UK population, groups characterized by low levels of education, income or social class have a higher prevalence of obesity. The Annual Health Survey for England 2002 estimates the average weight gain of the English population is about 0.35 kg/year, confirming a continuous upward trend [3]. An increase in fat mass does not only affect the life and the future health of adults, it is also a growing concern among children. Obesity manifests increasingly at a younger age and is affecting more and more children. According to a 2002 survey, more than 16% of US adolescents are overweight, and this number is rising dramatically [4]. These alarming figures show that obesity is no longer just a problem for the individual – it is now a problem for society and particularily for the health professional.

Causes of obesity

Obesity is usually caused as a result of increased energy intake and decreased energy output. Thus, the two major contributing factors are eating habits, consisting of an excessive intake of energy-dense foods and low levels of physical activity consequent to a sedentary lifestyle. These factors interact with specific genetic factors that predispose some individuals more than others to obesity. The reduction in energy expenditure is thought to be responsible for the fact that the UK self-reported kilocalorie intake from 1980 to 2000 has changed little while the incidence of obesity has risen [101]. Other causative factors are behavioral, environmental and genetic. It is important to note that single gene defects account for no more than 5% of morbid obesity [5]. Nevertheless, a polygenetic influence is likely and may have arisen due to the fact that evolutionary theory proposes that the genetic make up for modern man is designed to save him from death by famine (the 'thrifty gene theory').

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Table 1. Classification of weight based on BMI.

Classification	BMI (kg/m^2) Europeans	Classification	BMI (kg/m^2) Asian
Underweight	<18.5	Underweight	<18.5
Normal range	18.5–24.9	Normal range	18.5–22.9
Overweight	25–29.9	Overweight	Above 23
Obese Class I	30–34.9	At risk	23–24.9
Obese Class II	35–39.9	Obese Class I	25–29.9
Obese Class III	More than 40.0	Obese Class II	More than 30.0

BMI: Body mass index.
Adapted from International Obesity Task Force 2000 [53].

Adiposity-related risks

Obesity has adverse health effects and can lead to premature death [6]. Fat accumulation results in hormonal changes that lead to increased levels of fatty acids, estrogen levels and hyperinsulinemia. These in turn cause metabolic complications such as hypertension, dyslipidemia and glucose intolerance, leading to diabetes.

An exact calculation of obesity-related mortality is virtually impossible since it is an indirect cause of death. However, it is estimated that obesity reduces life expectancy by 3 to 14 years, primarily due to the increased risk of cardiovascular disease and cancers [7]. The mortality rate increases sharply for BMI values over 30 kg/m^2 [8,9] and is positively related to the duration of obesity. In the Framingham study population, the risk of heart disease was found to be increased by 15% in obese men and 22% in obese women [10]. A total of 75% of the obese subpopulation was hypertensive and more than two-thirds had hypercholesterolemia. A major component of obesity-related morbidity and mortality is determined by the onset of diabetes and diabetes-related macro- and microvascular complications. At diagnosis of Type 2 diabetes the average BMI is between 28 and 29 kg/m^2 [11]. Premature cardiovascular disease and death are well recognised risk factors of diabetes, independent of obesity. The mortality rates from coronary heart disease in people with diabetes are up to five-times higher and the risk of stroke up to three-times higher than in the general population [12]. The obesity-related mortality therefore increases substantially with concomitant diabetes and also with hypertension [13]. In contrast, weight loss can substantially decrease the mortality and morbidity of diabetes and hypertension regardless of the initial BMI. Obesity also leads to an increased risk of cancer, the most common obesity-associated cancers being hormone related such as endometrial cancer, breast cancer and prostate cancer but also colorectal cancer.

It has been estimated that between 15 and 20% of cancer deaths in the USA are associated with obesity [14]. Obesity negatively influences most body systems. It may cause gastrointestinal problems such as gastric reflux disease and gallstones as well as respiratory problems such as sleep apnea and obesity hypoventilation. Obesity can increase the risk of embolic disease and increases the anesthetic risk and postsurgical complications. It can cause or aggravate the polycystic ovary syndrome (PCO), which impairs ovulation and fertility. Diagnosing or investigating the concomitant health problems of patients with morbid obesity is complicated by the weight restrictions of some investigations, such as magnetic resonance imaging (MRI) and theater tables.

Last but not least, obesity is associated with psychologic and mental health problems, as well as problems with sexual function. Depression is far more common in the obese. Obesity can impact negatively on professional success and productivity. It is often accompanied by social stigma, further adding to the occupational disadvantage, and frequently leads to discrimination against and social isolation of the obese individual. According to a recent study by Viner obese men are not at risk of loss of income, but persistently obese women have a risk of never being employed (odds ratio [OR]: 1.9) and not having a current partner (OR: 2.0) [15].

Table 2. Waist circumference cut-off points for Caucasian subjects.

	Increased risk	Sunstantially increased risk
Men	>94 cm (37″)	>102 cm (40″)
Women	>80 cm (31″)	>88 cm (34″)

Adapted from World Health Organization [1].
Waist circumference cut-offs are specific to each ethnic group. For instance, South-Asian men are at increased risk when waist circumference exceeds 90 cm and women when it exceeds 80 cm.

Financial cost of obesity

The cost of obesity, including the UK National Health Service (NHS)'s expenditure on it can only be estimated, and this estimate will depend strongly on how the numerous indirect associations are accounted for. Obesity contributed to about 3.5 to 4% of the National Health Service (NHS) budget in 1998 and this percentage is rising [101]. Diabetes alone is estimated to account for 5 to 10% of the total health budget, 2.2 billion in 1997 [102]. In addition, there is a huge indirect cost to society such as the costs arising from sick leave.

Benefit of weight loss

In hypertensive obese patients, 1 kg of weight loss lowers the blood pressure (BP) by 1 to 2 mmHg [16]. Weight loss can prevent and delay the onset of Type 2 diabetes [17]. Modest weight loss of 5 to 10% over a 4-year period can more than half the new cases of diabetes and significantly reduce the risk of cardiovascular disease in overweight people [7]. In a diabetic patient, modest weight loss of 5 to 10% can improve glycemia and lipid levels as well as hypertension. Each kg of weight loss at 12 months after diagnosis is associated with an increased survival of 3 to 4 months [8], which is more than can be achieved with glucose, lipid or BP lowering alone. However, according to the UK Prospective Diabetes Study (UKPDS) 7, an average weight loss of 16% would be needed to normalize the fasting blood sugar from an initial 6 to 8 mmol/l to less than 6 mmol/l [18]. This is a far greater weight loss than can be achieved by most patients in order to 'cure' their diabetes. The effect of 10 kg of weight loss in a 100 kg obese patient has a substantial survival benefit (**Table 3**) [19]. The benefit of weight loss with consideration of cost effectiveness is usually expressed in Quality of Life (QoL) scores. QoL in obese people is lower than that of a general population in terms of physical function, general health status and vitality and is lower in obese women than men. QoL is inversely correlated to the degree of obesity and improves with weight loss, and it can normalize with substantial weight loss [20].

Prevention

Prevention of overweight and obesity is easier than treatment and should start at an early age. Health education regarding healthy eating and physical activity is increasingly promoted in schools. Government-led promotion of schemes such as 'five a day' (advice to eat five portions of fruit and vegetables a day) and the promotion of healthy school dinners are examples of more recent public concern. Those with a BMI of over 25 kg/m^2 should be targeted in particular, with additional counseling and screening for presence of comorbidities and signs of the metabolic syndrome, such as hypertension, hypercholesterolemia and glucose intolerance. Advice on losing weight through lifestyle changes with a combination of dietary and physical activity, is the first step in the treatment of the overweight and obese. Dietary advice should center on healthy eating and a kilocalorie deficit of 500/day, in order to facilitate sustained weight loss of 5 to 10 % of body weight at a rate of 0.5 to 1 kg/week.

Diet

There are a plethora of dieting regimes promoted either by commercial companies or medical professionals. Very low-calorie diets (VLCD) are usually commercially produced products that are the sole source of nutrition providing less than 800 kcal/day and marketed

Table 3. Benefits of 10 kg weight loss in a 100 kg subject.

Adiposity-related risks	Benefits of weight loss
Mortality	20–25% decrease in premature mortality
Blood pressure	10 mmHg decrease in systolic pressure 20 mmHg decrease in diastolic pressure
Lipids	10% decrease in total cholesterol 15% decrease in LDL-cholesterol 8% decrease in HDL-cholesterol 30% decrease in triglycerides
Diabetes	Reduces risk of developing Type 2 diabetes by 50% 30–50% decrease in elevated blood glucose 15% decrease in HbA1c

HDL: High-density lipoprotein; LDL: Low-density lipoprotein.

as a total food substitute. Their use has been reviewed in detail by Jebb and it is recommended that they should only be used under dietetic and medical supervision [21]. They have proven success in achieving significant short-term reduction in body weight. This is not sustained in the long-term and the use of these dietary aids are contraindicated in the following:

- Pregnant or breastfeeding women
- Cardiac disease
- Cerebrovascular disease
- Hepatic or renal disease
- Hyperuricemia
- Psychiatric disturbance
- Porphyria

Protein-sparing modified fasts (PSMF) are regimes that have a carbohydrate content of less than 40 g/day, irrespective of energy content. They offer no advantage to VLCD or low calorie diets (LCD) over 12 months and the same caution should be applied to PSMF as that with VLCDs. LCDs approximate to an energy intake of 1000 to 1600 kcal/day and low-fat diets (LFDs) facilitate reduction in total fat intake, which is the easiest way to reduce total energy intake by the necessary 500 kcal/day to reduce weight by 1.0 kg/week. Since the body has a large store of essential fatty acids and the absolute requirements for these nutrients are very small, the percentage of energy from fat in a LFD can be as low as is practicably possible. Patients following LCD or LFD do not sustain initial weight loss at 12 months. Low carbohydrate diets of 20 to 40 g carbohydrate/day, the most popular being The Atkins Diet, are not recommended by the British Dietetic Association and Dieticians in Obesity Management unless under dietetic and medical supervision, and then only for a short period of time [103]. When they are used, initial weight losses are not maintained at 12 months. Meal replacement (e.g., Slimfast®, Cambridge Diet®) is another approach used in the treatment of obesity and the products are usually available over the counter. There is no official definition of this approach but meal replacements are generally considered to be portion-controlled products that are vitamin and mineral fortified and replace one or two meals in the day allowing one low kilocalorie meal using standard foods. This type of regime will usually provide 1200 to 1600 kcal/day and the products are not expected to be the sole source of nutrition. Other popular diets include Weight Watchers, Slimming World, Mediterranean, and Glycemic Index. Whilst not having scientific evidence of efficacy, such regimes are not of themselves deemed to be inappropriate nutritionally. Data from a systematic review of randomized controlled trials of the long-term benefits of weight-reducing diets in adults does not support the use of anything other than LFDs for weight reduction in obese adults [22]. It is current best practice to combine a LFD with the Government's guidelines on healthy eating, 'The Balance of Good Health' [23], and for motivational interviewing to be employed. The key characteristics for successful dietary weight control are listed in **Box 1** [7].

Behavior modification

Whilst there is consensus that the basis of a well-structured approach to treating obesity consists of diet, physical activity and behavior modification, reliable conclusions about behavior modification cannot be drawn from the published literature [20]. However, some components of behavior modification are used with success and they include developing social skills (saying 'no' to food without guilt or anxiety) and controlling signals and behavior that leads to obesity.

Physical activity

There is no consistent evidence that an increase in physical activity prevents weight gain but those who exercise the most are the least likely to be obese [24] and gain less weight as they get older [25]. Young people who are the most sedentary are more likely to become obese [26].

Box 1. Key characteristics of successful dietary weight control.

- Low fat foods
- Proportionally more carbohydrates
- Reduced fat cooking methods
- Smaller portion sizes
- Restricted intake of energy dense foods
- Regular meals and snacks
- Increased fruit and vegetable intake
- Increased physical activity
- SMART goals set
- Regular weighing
- Information obtained from a variety of sources to devise personal weight loss strategies
- Help and support from family, friends and health professionals

Adapted from Jebb, 2003 [7].
SMART: Specific, Measurable, Achievable, Realistic, Timed.

However, physical activity alone is less effective than dietary treatment [20]. Physical activity reduces abdominal fat and prevents further weight gain [27]. The combination of behavior therapy, physical activity and diet is more effective than either alone and are therefore used together in therapeutic lifestyle change programs. Irrespective of the weight effect of physical activity, it does substantially decrease the risk of Type 2 diabetes [28]. Moderate exercise for 30 min at least three to five times/week, if not daily, is currently recommended. Examples of adequate physical activities are listed in **Box 2**. These levels of activity are equivalent to using 150 to 200 kcal, depending on the patient's weight and the level of activity, which is the approximate equivalent of a single glass of wine.

Drug therapy

The history of antiobesity drug development starts with several failed products that were withdrawn consequent to their side effects. Fenfluramine and dexfenfluramine were withdrawn in 1997 as heart valve problems were recorded and sudden deaths had occurred.

Phentermine, a centrally acting catecholaminergic drug, was licensed for periods of up to 12 weeks alongside conservative treatments. Its use is no longer indicated for routine management of weight loss, particularly as there are other drugs suitable for longer term use. Also, the weight loss with fenfluramine and phentermine was only transient, and at the cost of side effects such as insomnia, nausea, vomiting, diarrhea, dizziness, depression and risk of abnormal heart rate [16]. Methylcellulose, a bulk-forming drug, was thought to increase the feeling of satiety and help weight loss, but randomized controlled trials did not confirm weight reduction. At present there are only two drugs whose use is recommended by the National institute of clinical excellence (NICE) – orlistat and sibutramine.

Box 2. Examples of moderate amounts of physical activity.

Common chores
- Gardening for 30–45 min
- Raking leaves for 30 min
- Washing and waxing a car for 45–60 min
- Washing windows or floors for 45–60 min
- Stair walking for 15 min

Sporting activities
- Walking 1¾ miles in 35 min (20 min/mile)
- Running 1½ miles in 15 min (10 min/mile)
- Swimming laps for 20 min
- Cycling 5 miles in 30 min
- Dancing fast (social) for 30 min

Adapted from the National Institute for Health and Clinical Excellence, 2000 [101].

Orlistat became available in September 1998. It is formulated in capsules of 120 mg, which are taken three times a day. It is an inhibitor of pancreatic and intestinal lipases and prevents absorption of about a third of the fat that passes straight through the bowel (in comparison with 5% with placebo). As a consequence of this fat transit, it causes unwanted effects such as fatty or oily feces (20% of patients), fecal urgency (22%), flatus with discharge (24%) and oily spotting of underwear (27%), which are worse if the patients do not adhere to a low-at diet [29]. The side effects become less common with longer duration of drug use. Although circulating levels of fat-soluble vitamins (vitamins A, D, E and K) are reduced slightly, this is not thought to be clinically significant and vitamin supplements are not routinely recommended. Orlistat is systemically absorbed to a very small extent, but its use is not recommended in pregnancy, childhood or if breastfeeding. It is contraindicated in malabsorption syndromes and cholestasis. Orlistat improves cardiovascular risk factors by improving blood lipids, glucose metabolism and reducing BP [30]. The Cochrane review of 11 long-term studies (minimum follow-up period of 1 year) identified 2.7 kg (2.9%) more weight loss compared with placebo [104]. Continuation of treatment beyond the first 3 months is made on the basis of response to and adverse effects associated with treatment at that point. Thereafter treatment can be continued so long as the patient continues to show benefit and there are no adverse effects. Currently NICE guidance recommends stopping treatment after 1 year or exceptionally after 2. However, in individual cases the clinician has to make a judgement on benefits of continued therapy, as regain of lost weight may be particularly deleterious to those with comorbidities.

Sibutramine was originally developed as an antidepressant. It acts in the brain where it inhibits reuptake of norepinephrine and serotonin, and to a minor extent dopamine. It alters the appetite threshold by increasing the feeling of satiety. It is generally well tolerated, but can increase BP levels in some patients. BP therefore

requires regular monitoring. Other side effects include dry mouth, constipation, insomnia and nausea, which were more than twice as common in the treatment versus placebo group in the Sibutramine Trial of Obesity Reduction and Maintenance (STORM) study [31]. Sibutramine is contraindicated in uncontrolled hypertension, ischemic heart disease, arrhythmias, congestive heart failure or stroke. Overall weight reduction as result of a meta-analysis at 12 months is 4.12 and 3.40 kg at 18 months [32]. The Cochrane meta-analysis of five studies determined 4.3 kg (4.6%) more weight loss with sibutramine than with placebo [104]. Treatment with sibutramine also improves the lipid profile and glucose metabolism.

Limitations of currently recommended drug therapies

NICE recommends starting pharmacologic antiobesity treatment in clinics that have multi-disciplinary support available and using orlistat after all other conservative treatment modalities have failed. Both drugs are to be started if BMI is more than 30 kg/m^2 or there is presence of one or more comorbidities which increase the health risk of obesity (e.g., hypertension, diabetes). In this case orlistat treatment can begin with a BMI of 28 kg/m^2 and sibutramine treatment with a BMI of 27 kg/m^2. Evidence of benefit is lacking above the age of 65 years for sibutramine and 75 for orlistat. The drugs should be discontinued if follow-up visits do not demonstrate sufficient weight loss (so called 'therapeutic hurdles') and, following current guidelines, stopped at 12 months (sibutramine) and never continued for more than 24 months (orlistat) as evidence and data on cost effectiveness is poor. The dropout rate in the first 12 months of treatment in clinical trials is 33% with orlistat and 43% with sibutramine [104]. For both regimens, frequent follow-up visits are required; however, many of these patients would attend their general practioner (GP) or hospital doctor for comorbid conditions. Hypertension is one of the side effects of sibutramine, BP needs to be monitored. Treatment must be discontinued if BP rises by more than 10 mmHg (systolic or diastolic) or heart rate increases by more than 10 beats/minute. In those in whom such a rise in BP does not occur (most of those treated), BP would reduce with weight loss. Sibutramine treatment is associated with an increase of high-density lipoproteins (HDL) and lower triglycerides, whereas orlistat lowers low-denisty lipoprotein (LDL)-cholestrol as well as BP. Further long-term studies are required for to examine whether the same weight loss achieved with different treatments give the same beneficial effect on cardiovascular risk [32]. There are many patients who do not respond or are not suited for either of these two drugs. There is therefore a need for more drugs to treat obesity, particularly when associated with other cardiovascular risk factors.

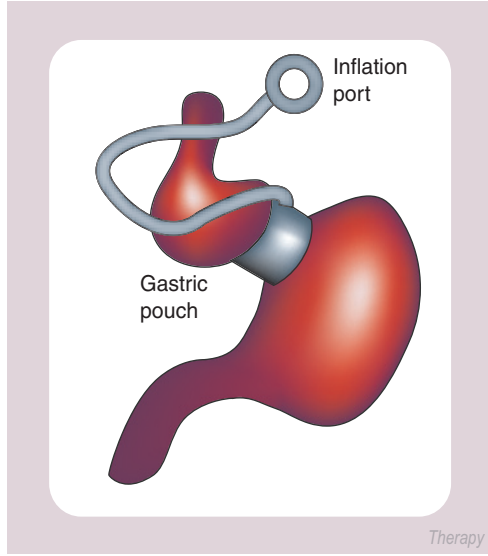
There are no pharmacologically recommended safe agents for children with obesity in the UK, although in the USA orlistat is now licensed for use in adolescents with obesity. Such therapy should therefore only be offered by pediatricians with expertise in obesity management (of which there are few in the UK).

Agents approved for other indications but supporting weight loss

The UKPDS showed favourable outcomes for metformin treatment of overweight, Type 2 diabetic patients [11]. It has since become the first choice for diabetes management of obese diabetic patients. Metformin decreases mortality after 10 years in obese people with Type 2 diabetes [22]. Unlike most other diabetic treatments (including insulin), metformin does not cause weight gain. It has gastrointestinal side effects such as nausea and diarrhea, which may explain some weight loss, and thus is poorly tolerated at maximum doses. Approximately 5% of adults cannot tolerate metformin at all. However, the weight deficit is not enough to pass the drug as an antiobesity agent. While a weight loss of 1.09 kg at 12 months was observed, no benefit over diet was observed in the long-term (e.g., 15 years in the UKPDS [11]).Though metformin will never become an antiobesity drug *per se*, it has a wider indication for the use within obesity. Aside from its glucose-lowering effect, it significantly reduces total cholesterol (-0.72 mmol/l over 24 months) [33]. Metformin is increasingly finding its place into fertility treatment of anovulatory PCO and ovulation induction [34], which is a condition strongly associated with obesity.

The selective serotonin reuptake inhibitors (SSRIs) fluoxetine and sertraline are antidepressants with appetite-suppressing effects. The available evidence at 12 months of treatment supports a weight loss of 0.33 kg [22]. Though this weight deficit is insufficient to

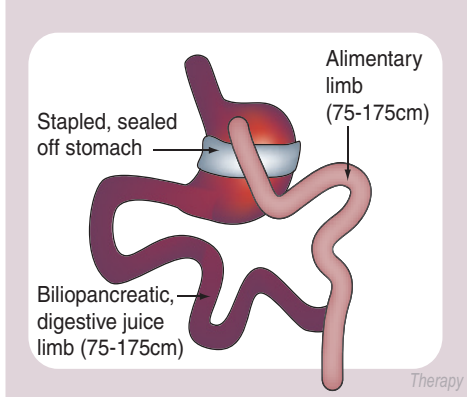
Figure 1. Laparoscopic gastric lapband.



support long-term use of this medication for the sole indication of weight reduction, the obese patient with depression will benefit, especially as their natural weight history will be to gain weight. Bupropion is an inhibitor of norepinephrine, serotonin and dopamine (not an SSRI). It is currently licensed as an antidepressant and for the treatment of smoking cessation but not for the use of weight loss, though it does have a considerable, but variable, antiobesity effect [35].

The wider known antiepileptics like valproate, gabapentin and carbamazepin are associated with increased body weight, whereas some antiseizure drugs support weight loss. For example, topiramate and zonisamide were tested in clinical trials. A considerable drawback of topiramate is its profile of adverse events (e.g., cognitive dysfunction) which have not yet been overcome by pharmacotechnology. Zonisamide is better tolerated and shows a greater weight reduction in a 16-week trial [36].

Figure 2. Roux-en-Y gastric bypass.



Surgical options

Bariatric surgery (surgery aimed at weight loss, the term derived from the Greek words 'baros' meaning weight and 'iatrikos' the art of healing) can be of a stomach-restrictive type or combined with a procedure resulting in malabsorption. The most widely practised procedures are gastric banding, gastric bypass and biliopancreatic diversion, other procedures having been superseded.

Vertical & horizontal gastroplasties & intragastric balloons

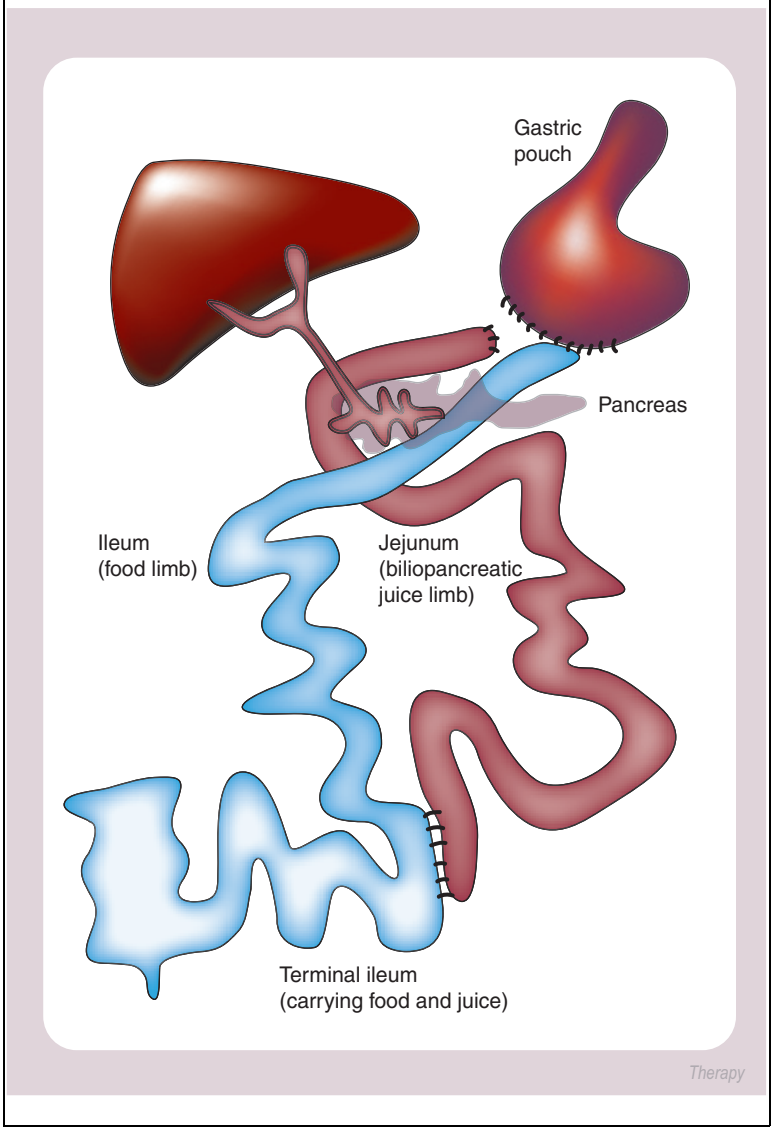
The use of stapled gastroplasties, intragastric balloons, and jaw wiring, have been superseded by other procedures and are not now normally used in the treatment of obesity.

This restrictive operation uses a silicone band to compartmentalize the stomach into small proximal and large distal segments (**Figure 1**). The band has a subcutaneous reservoir such that if weight loss plateaus, the upper gastric segment can be adjusted. In a study of 454 patients who underwent laparoscopic gastric banding, the average weight loss after 1 year was 35.5 kg and mean excess weight loss was 72% after 3 years [37]. Another study of 300 patients reported weight loss of at least 50% in 60% of patients after 2 years and BMI stabilized between 30 and 31 kg/m^2 [38].

Gastric bypass

Several randomized controlled trials and other long-term follow-ups have shown that gastric bypass (GBP) results in greater weight loss than other forms of gastroplasty. It is considered to be the standard against which other surgical methods can be compared [20]. The procedure produces a combination of restricted intake of food and malabsorption of the food. A small pouch is created in the upper portion of the stomach and anastomozed to the proximal jejunum, excluding most of the stomach (**Figure 2**). The small bowel is shortened by 150 to 300 cm depending on the BMI of the patient. A prolonged feeling of fullness and modest malabsorption is produced. There are fewer complications than with more radical procedures such as jejunoileal bypass. However, there is a risk of iron, calcium and vitamin B12 depletion. Dietetic input, both pre- and postoperatively, is crucial as considerable changes

Figure 3. Bileopancreatic diversion and duodenal switch.



in diet and monitoring of nutritional status are required. Gastric bypass results in weight loss of approximately 33% 2 years postoperatively [39].

Bileopancreatic diversion & duodenal switch

The bileopancreatic diversion is a restrictive and malabsorptive procedure that does not have a 'blind' intestinal limb where bacterial overgrowth can occur. The duodenal switch was developed from the bileopancreatic diversion and divides the duodenum in the distal bulb and the ileum proximal to the ileocacal valve, with anastomosis of the proximal duodenal segment to the distal ileal segment (**Figure 3**). It is hoped that this will prevent the protein malnutrition, calcium deficiency and fat-soluble deficiencies associated with the bileopancreatic diversion.

Limitations & benefits of surgical treatment

Surgery is considered the last resort and is only available for the morbidly obese (BMI >40 kg/m^2, or 35–40 kg/m^2 with existing comorbidities). It is offered only to individuals above the age of 18 years, who are fit for anesthesia and surgery, after all other treatments have failed. Nevertheless, it is the most successful method with the most weight loss after 10 years of intervention. Surgery is very effective in improving insulin sensitivity with bypass procedures giving more improvement than restrictive procedures. Bypass procedures produce a more rapid resolution of diabetes [40], which could be at least partially related to a favorable change of gut hormones that regulate insulin secretion and appetite.

The Swedish Obese Subjects (SOS)-trial, a nonrandomized trial comparing surgery versus nonsurgical controls, shows a 35 kg weight loss with surgical treatment versus no weight loss at 2 years. Those with a BMI of more than 40 kg/m^2 reduced their plasma insulin by 60%, their fasting plasma glucose and triglycerides by 25% and BP by 10% [41].

Surgical mortality is estimated at 1% and complications at 2 to 10%. However, one should be aware of the potential risk of death with surgery, though only small, and other considerable side effects which vary depending on the type of surgery. Laparoscopically performed gastric banding may prove to be the safest procedure, with one of the best success rates, but further research and cost analysis are required.

Treatment costs

In health economy analyses, obesity needs to be viewed within the context of obesity-related disease. Calculations of obesity-related costs are only estimates, especially as the available long-term data on health outcomes for obesity intervention and treatments have, in general, only evaluated 2-year follow-up studies (5 years for surgical interventions). Orlistat costs GBP£0.49/capsule and is estimated to cost GBP£537/year if taken at the recommended dose of three capsules a day. Sibutramine costs GBP£35 to 39 for 28 days depending on the dose used, which equals GBP£456 to 510/year. The cost of staff (e.g., practice nurses, dieticians) for consultation and referral to pharmacologic and behavior therapy must be added to these totals. These include primary as well as secondary care and tertiary level, due to the

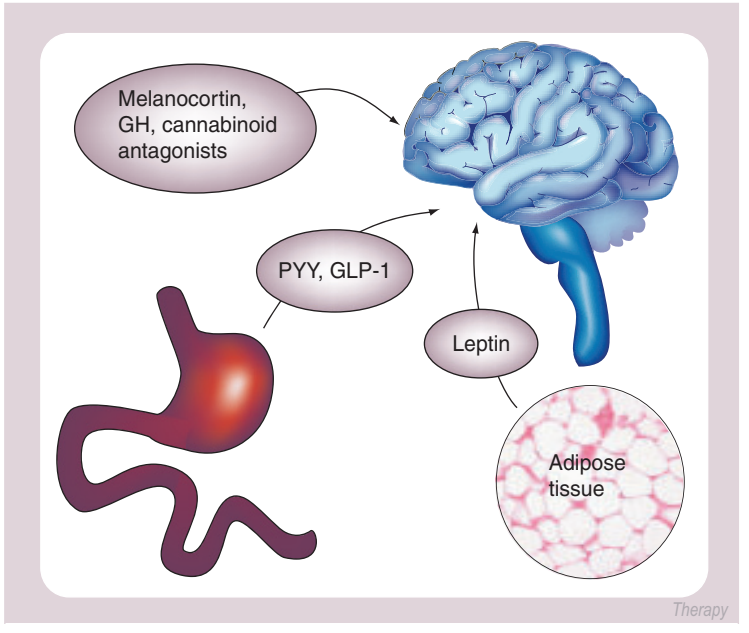
'knock on' effect on all healthcare services. As a measure of cost effectiveness, economic evaluations of weight therapy are based on the cost per quality-adjusted life year (QALY). Lifestyle interventions have the poorest performance with this measure, unless they are targeted at high-risk patients [32]. The QALY for drug and surgical treatments targeting high-risk patients is no more than GBP£13,000. Surgery, which is targeted at morbidly obese and glucose-intolerant subjects, is shown to be most cost effective, with a QALY of GBP£2329/additional life year.

New developments & hopes

The recent discovery of many orexigenic (appetite-stimulating) and anorexigenic (appetite-reducing) hormones, and a better understanding of central hypothalamic appetite regulation (**Figure 4**), has opened the door to new drug development. Several pharmacologic therapies are currently in clinical trials and some of them are likely to be on the market soon.

Investigations into the molecular basis of effects of endogenous cannabinoids, suggest they may be promising agents for the treatment of obesity. Selective antagonism of the cannabinoid Type 1 receptor (CB1) reduces the motivation to eat. The weight-loss effect is mediated by a central action on the hypothalamic appetite regulating centers and peripheral fat mass regulating mechanisms. The cannabinoid receptor antagonist compound (rimonabant) is currently in Phase III clinical trials in Europe and North America [42]. Adverse events may include mood disturbance and some gastrointestinal problems at highest doses but rimonabant is generally well tolerated with a favorable effect on the lipid profile. There are currently no data on long-term treatment. Rimonabant is also an effective facilitator of smoking cessation [43].

Figure 4. Neuroendocrine appetite suppressants.

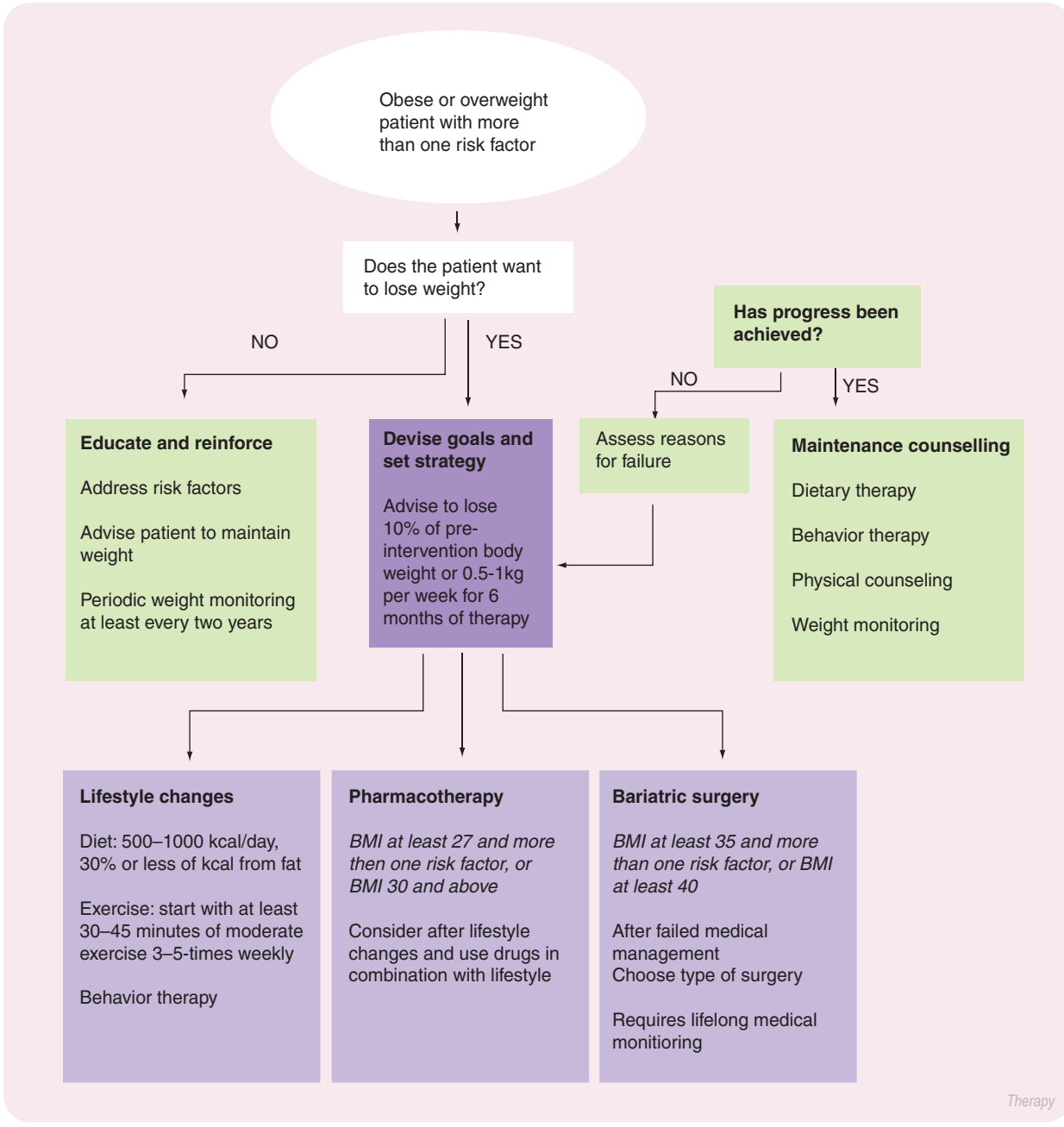


Leptin (Greek: "thin") is a hormone secreted from adipose tissue. It was discovered in 1994 and is the 'big hope' for antiobesity therapy. Serum leptin levels are directly correlated with the amount of fat mass. Recombinant leptin can be administered by subcutaneous injection and leads to a dose-dependent reduction of body weight. Unfortunately, the weight-reducing effect of leptin is largely limited to rare genetic types of congenital leptin deficiency [44]. A resistance to the central actions of leptin, particularly at the blood–brain barrier, is postulated in obesity [45]. Consequently, further leptin administration has little effect in the obese and leptin-resistant state. In order to overcome this resistance, leptin analogs, which cross more easily into the cerebrospinal fluid, have been developed. Initial clinical trials report promising results, with a weight loss of 5 kg in the first 6 months.

Polypeptide Y (PYY) is a gut hormone, which reduces appetite through central action at the level of the hypothalamus and also delays gastric emptying. Its levels are reduced in human obesity. The exact mechanism for this decline is not known. PYY increases after gastric bypass surgery, which may contribute to the decreased appetite observed after this type of surgery [46]. Intravenous administration of PYY to human obese subjects reduces appetite by 30% and reduces weight gain. Unlike leptin, there is no resistance to its action [47]. Further exploration into its potential as obesity medication, and the effect of long-term administration, is needed.

Glucagon-like peptide-1 (GLP-1) is a gut hormone that releases insulin from the pancreas after the ingestion of nutrients. Such insulin-releasing hormones are called incretins. For this reason, GLP-1 analogs are promising agents for the control of blood sugar in Type 2 diabetes. They may also have a role in obesity therapy as they cause satiety signaling in the hypothalamus and a delay of stomach emptying. GLP-1 secretion decreases in obese patients but weight loss normalizes its levels. Intravenous administration of GLP-1 reduces food intake in lean and obese subjects by

Figure 5. Algorithm of obesity treatment.



Evidence-based algorithm for obesity treatment.
BMI: Body mass index.
Adapted from the National Institute for Health and Clinical Excellence, 2000 [101].

12% [48]. This suggests GLP-1 analogs (e.g., exanatide and liraglutide) have the potential to become successful obesity treatments. However, there is a potential danger of hypoglycemia with GLP-1 administration in nondiabetic subjects [49] and, therefore, its use may need to be reserved for only obese patients with diabetes.

GLP-1 and PYY are inactivated by the enzyme dipeptidyl peptidase (DPP)-IV. DPP-IV inhibitors increase the levels of active GLP-1 and PYY. Their antiobesity and antidiabetic effects are being assessed separately.

The importance of the melanocortin (MC) system in obesity has been confirmed by the

recent discovery of mutations in the MC4 receptor in morbidly obese patients. Intranasal administration of a fragment of MC decreases body fat in humans [50]. Its weight-reducing potency in obese individuals needs to be specified, and research into the MC pathways is ongoing.

The growth hormone (GH)–insulin-like growth factor (IGF) axis is disturbed in obesity, which is a state of low circulating GH and low-normal to normal-free IGF 1 concentrations. Obese individuals have an increased sensitivity to recombinant GH [51], and GH treatment leads to a reduction in fat mass and increased lean body mass. A clinical trial using recombinant human GH treatment versus placebo for obesity management, shows a modest weight loss of 2 kg in 6 months with a high dropout rate [52]. Though these results show an only modest effect on weight loss, the GH axis and its modulation remain possible targets for obesity management. Drugs such as the advanced obesity drug (AOD) 9604 are in development. They mimic metabolic properties of human GH and enhance lipolysis, whilst avoiding systemic effects.

Highlights

- Obesity is a chronic, progressive and relapsing disease.
- Modest weight loss of approximately 10% brings significant health benefits.
- Lifestyle modification should be offered to all patients with obesity first, preferably delivered by a multidisciplinary team.
- Drug therapy may be appropriate in those unable to achieve weight loss with lifestyle changes alone.
- Surgery should be considered in those who are unsucessful with all medical approaches to obesity management, especially when there are significant comorbidities.

Expert commentary & outlook

Obesity is a chronic, progressive and relapsing disease and its management is a challenge. The consequences of the worldwide obesity epidemic are a serious threat to the QoL and health of individuals, and eventually to the economy of industrialized and developing countries. Obesity is acquired through a chronic state of positive-energy balance. Weight loss and weight maintenance by lifestyle changes (diet and physical activity) require continuous motivation and support. However, patient compliance is inconsistent even if support is available. The effects of the available pharmacologic aids to weight loss are insufficient and transient. Bariatric surgery is currently the most effective measure, but it is not a general solution to the problem, only a treatment for morbid obesity (in which many obesity-associated health problems are already manifest) and in the UK, it is only available in limited number of centers. An algorithm of today's obesity treatment is shown in **Figure 5**.

There is an urgent need to continue development of new more effective agents that are well tolerated and suitable for widespread use. The diabetes epidemic which will inevitably follow the current obesity epidemic demands that action be taken, and that there is an increase in research to find a solution appropriate to the current environmental pressures that drives weight gain. Recent discoveries and increased knowledge into the regulation of energy homeostasis are encouraging and there is increasing optimism in the field.

Information resources

- British Dietetic Association. www.bda.uk.com/Downloads/Dietitians_Publ_Control.pdf (Accessed October 2005)
- DOM (UK) Position statements. www.domuk.org (Accessed October 2005)

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Affiliations

Katarina Kos, MRCP,
Clincal Research Fellow
Clinical Sciences Research Institute,
University Hospital of Coventry & Warwickshire & Warwick Medical School
Coventry CV2 2DX, UK
Tel.: +44 247 657 4665
Fax: +44 247 657 4871
katarina.kos@warwick.ac.uk

Christine Baker, MScRD,
Specialist Morbid Obesity Service
University Hospital of Coventry & Warwickshire
Coventry CV2 2DX, UK
Tel.: +44 247 657 4665
Fax: +44 247 657 4871
dietaryadvice@aol.com

Sudhesh Kumar, MD, FRCP,
Professor of Medicine & Honorary Consultant Physician
Clinical Sciences Research Institute,
University Hospital of Coventry & Warwickshire & Warwick Medical School
Coventry CV2 2DX, UK
Tel.: +44 247 657 4665
Fax: +44 247 657 4871
sudhesh.kumar@uhcw.nhs.uk